HEALEY ALS Platform Trial

Sabrina Paganoni, MD, PhD
Ben Saville, PhD

Jinsy Andrews, MD; Jeremy Shefner, MD, PhD; James Berry, MD, MPH; Eric Macklin, PhD; Melanie Quintana, PhD; Kristine Broglio, MS; Michelle Detry, PhD; Merit Cudkowicz; MD, MSc

MASSACHUSETTS GENERAL HOSPITAL

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

HARVARD MEDICAL SCHOOL

1. Why Now?

2. Why Platform?

   Scientific and Statistical Advantages

3. **HEALEY ALS Platform Trial**

ALS is the neuromuscular disease with the **largest drug pipeline**

- Over 130 companies in ALS space
- Thousands of investigators worldwide - many targets

"I lost the privilege of working on the human time clock on January 6, 2018 – the ALS clock is a lot faster"
Sandy – Person with ALS

- Platform approach decreases time to finding effective therapies

When will we find first effective therapy?

Years

Traditional

Platform

**Assumes 10% of therapies tested are effective with a 30% slowing in rate of progression*

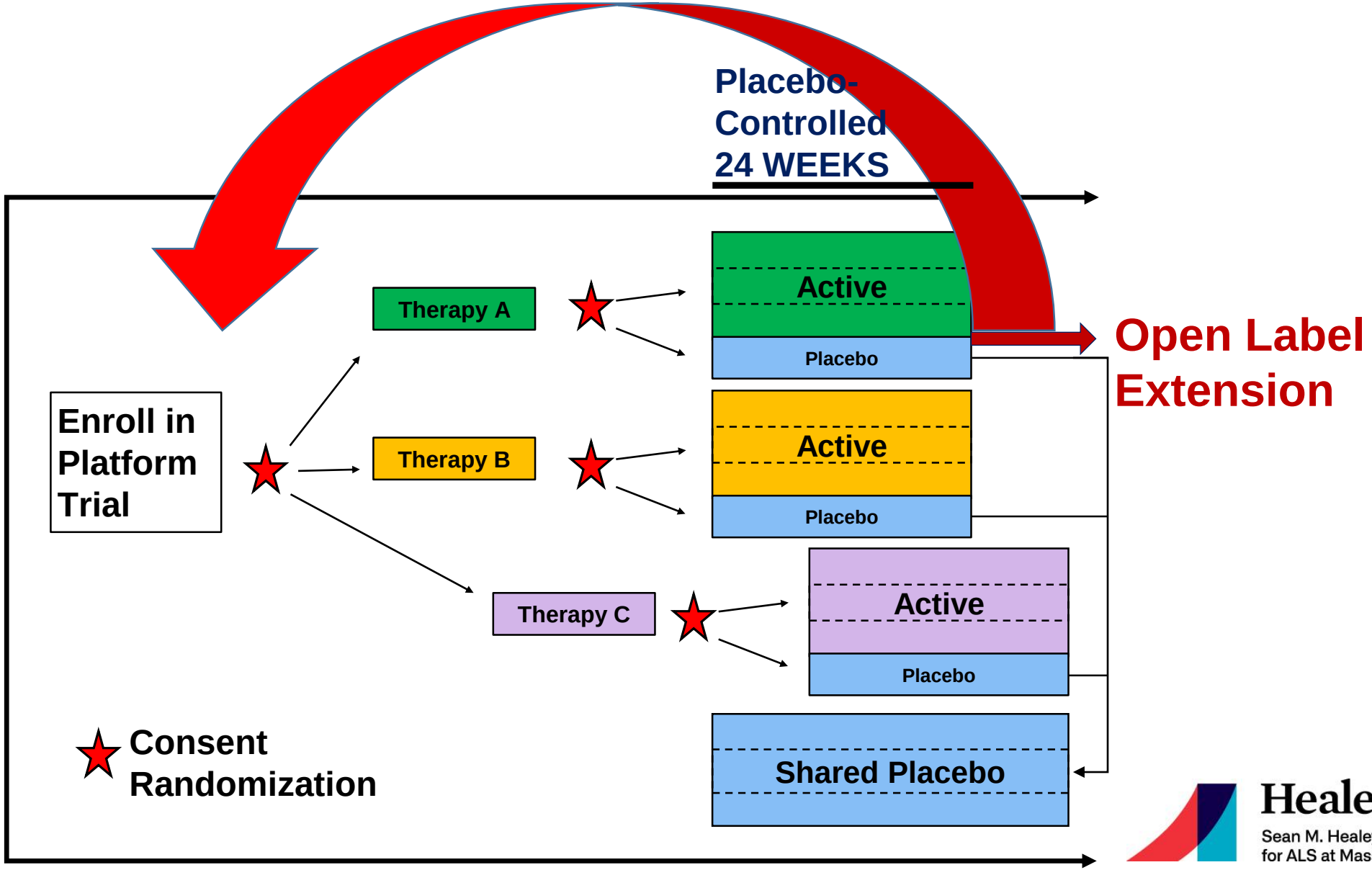
Traditional

	Intervention
Disease	Therapy A

Platform

	Intervention		
Disease	Therapy A	Therapy B	Therapy C

Less placebo, more access, more options



Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

ENDPOINTS

Primary Endpoint

Change in disease severity - **ALS Functional Rating Scale-Revised (ALSFRS-R)**

Secondary Endpoints

1. Change in respiratory function - slow vital capacity (SVC)
2. Change in muscle strength - hand held dynamometry (HHD)
3. Survival
4. Treatment-specific biomarkers as applicable

Exploratory Endpoints

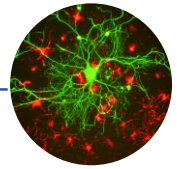
Safety Endpoints

Exploratory Endpoints

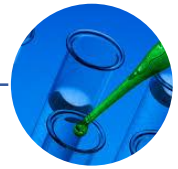
Endpoint Development Engine

DNA

Neurofilaments



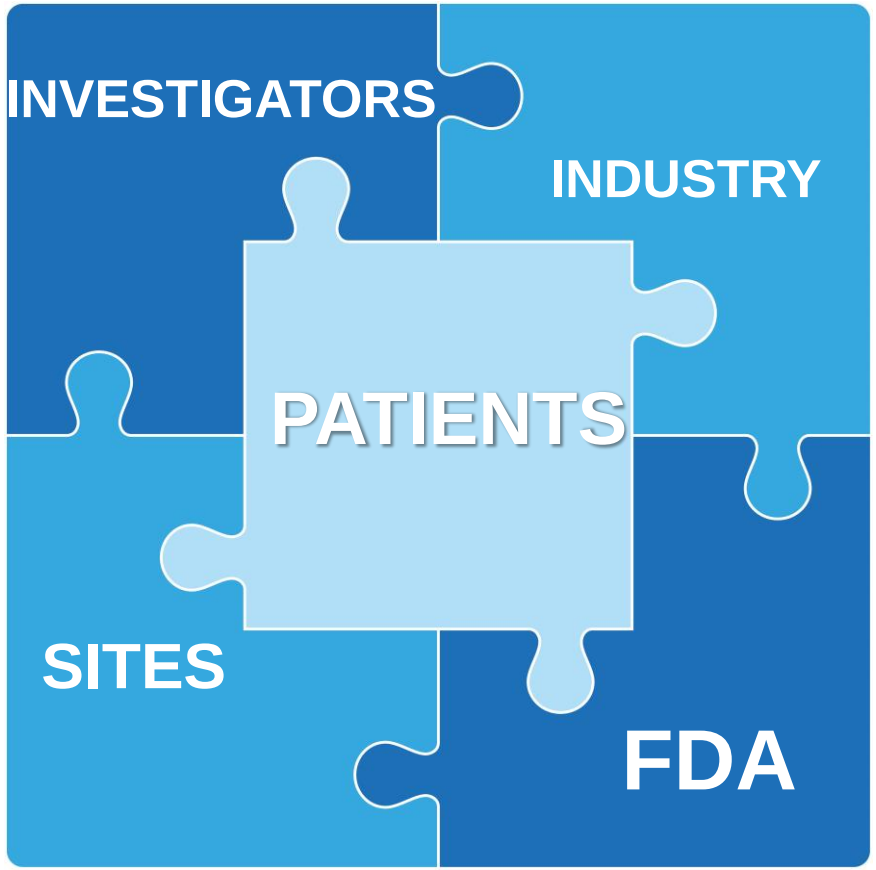
PBMCs > Stem Cells



Biomarkers (Blood, Urine, CSF)

Speech / Digital

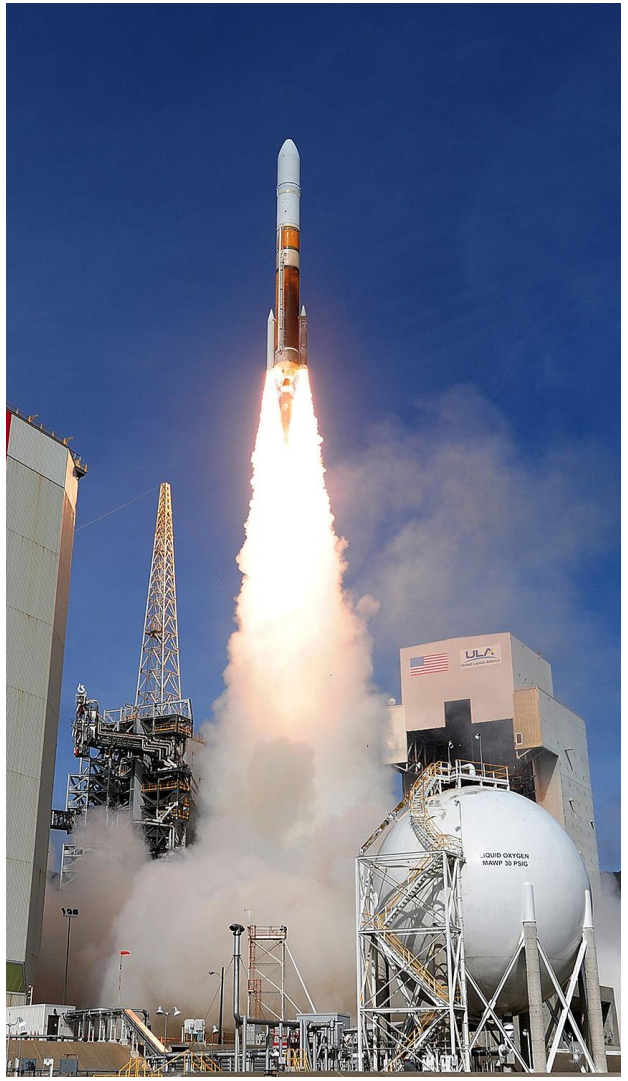
Bringing together a community to launch the first platform trial for ALS very fast



Concept to Launch

1 Year

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General



ENGAGED TRIAL DESIGN COMMITTEE

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

Jinsy Andrews

James Berry

Merit Cudkowicz

Sabrina Paganoni

Jeremy Shefner

Eric Macklin

Berry Consultants
Statistical Innovation

Melanie Quintana, PhD
Kristine Broglio, MS
Michelle Detry, PhD
Ben Saville, PhD

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

NEALS Advisory Panel

Senda Ajroud-Driss	Americo Fernandes	Erik Pioro
Ettore Beghi	Angela Genge	Jeffrey Rosenfeld
Michael Benatar	Matthew Harms	Zachary Simmons
Robert Bowser	Bjorn Oskarsson	Nimish Thakore
Amy Chen	Steve Kolb	David Walk
Sheena Chew	Shafeeq Ladha	Jim Wymer

Experienced Clinical Operations Team

Marianne Chase
NCRI Project Management

Annette DeMattos
NCRI Grants & Contracts

Megan Hall
BNI Monitoring & Outcomes training

Alex Sherman
NCRI Clinical Trial Systems

Hong Yu
NCRI Data Management

Eric Macklin
MGH Biostatistics

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

BARROW Neurological Institute®

NCRI NEUROLOGICAL CLINICAL RESEARCH INSTITUTE

- Raji Bhat
- James Chan
- Derek D'Agostino
- Catherine Gladden
- Brittney Harkey
- Katie Jentoft
- Lindsay Pothier
- Rebecca Randall
- Melissa Ricker
- Aileen Shaughnessy
- Lisa Spagnuolo
- Eric Tustison
- Jason Walker

54 TRIAL-READY SITES

1 Central IRB

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

20+ years experience; 57 ALS studies with >20K participants already completed including 21 industry-sponsored trials

Patient Engagement

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

"Platform trials may possibly be the best thing I have seen since diagnosis!"

"Thank you for ensuring that patient voices are involved in every facet of this effort"

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

MASSACHUSETTS GENERAL HOSPITAL

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

Therapy Selection: Selection Committee
From Healey and NEALS Science Advisory Committees

Request for Proposals (RFP)

- Almost 30 applications from 10 countries
  - industry and academic
- Five were selected to enter the platform now

How to Participate:

https://www.massgeneral.org/neurology/als/research/platform-trial

Zilucoplan – complement C5 inhibitor

Verdiperstat – myeloperoxidase inhibitor

CNM-Au8 – gold nanocrystals

Pridopidine – Sigma 1 Receptor agonist

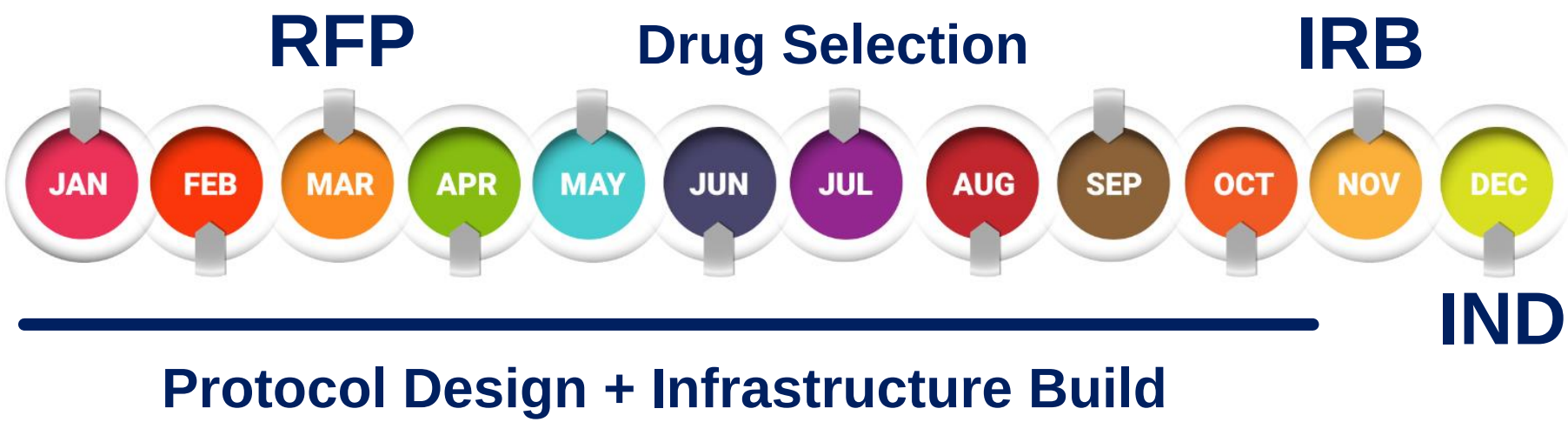
IC14 – immunotherapy targeting CD14

Partnership with the FDA: very positive meetings IND submission 12/2019

- **July 9, 2019** – FDA Type C Meeting in Washington DC

- **November 5, 2019** – Brought three companies together to meet with us and the FDA to finalize the HEALEY ALS Platform trial design.

Concept to Launch = 1 year



Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

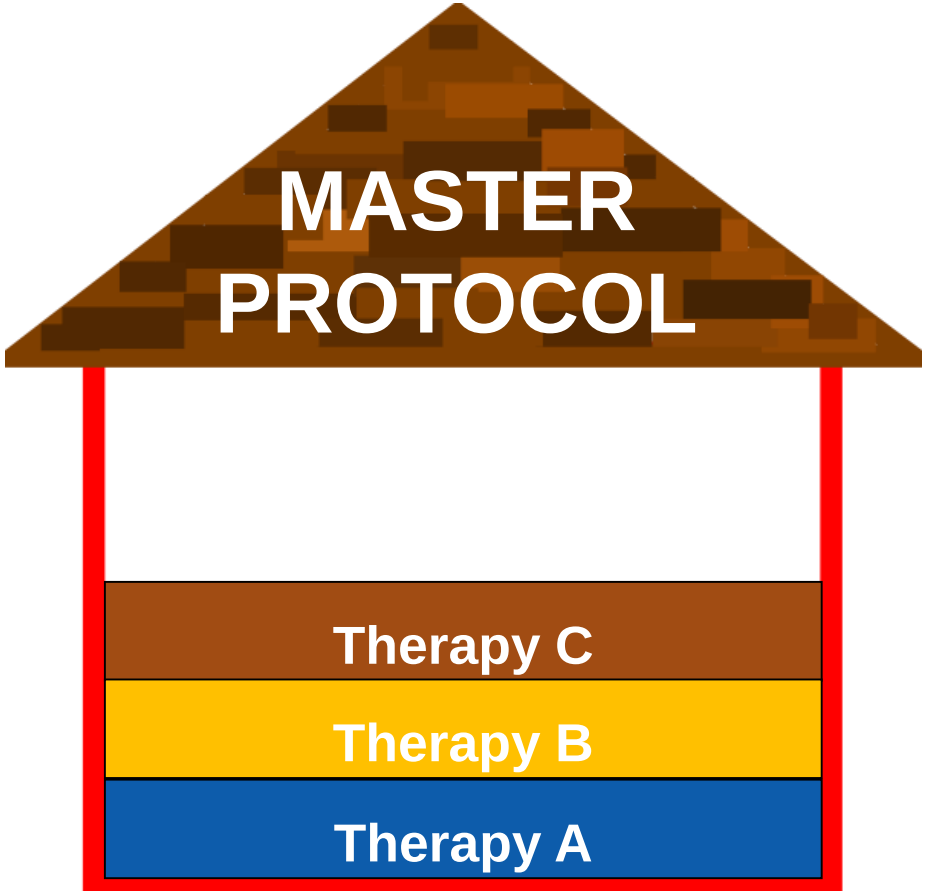
Berry Consultants
Statistical Innovation

Melanie Quintana, PhD
Senior Statistical Scientist

Kristine Broglio, MS
Director & Senior Statistical Scientist

Ben Saville, PhD
Senior Statistical Scientist

Michelle Detry, PhD
Director, Adaptive Trial Execution &
Senior Statistical Scientist



ALS Platform Trial

The trial is governed by a **Master Protocol** – a common protocol for multiple therapies

- Defines global rules that govern the therapies being investigated and how participants flow through the trial

Appendix: The mechanism through which therapies are added to the platform and attached to the master protocol

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

From the Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD. Address reprint requests to Dr. LaVange at the Office of Biostatistics, Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Blvd., Silver Spring, MD 20993, or at lisa.lavange@fda.hhs.gov.

N Engl J Med 2017;377:62-70.
DOI: 10.1056/NEJMra1510062

HIGH-QUALITY EVIDENCE IS WHAT WE USE TO GUIDE MEDICAL PRACTICE. The standard approach to generating this evidence — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. As a result, important clinical questions go unanswered. The conduct of "precision medicine" trials to evaluate targeted therapies creates challenges in recruiting patients with rare genetic subtypes of a disease. There is also increasing interest in performing mechanism-based trials in which eligibility is based on criteria other than traditional disease definitions. The common denominator is a need to answer more questions more efficiently and in less time.

A methodologic innovation responsive to this need involves coordinated efforts

Master Protocol Overview

- **Primary Endpoint**
  - Change in disease severity through 6 months
  - ALS Functional Rating Scale-Revised (ALSFRS-R)
- **3:1 randomization** for each therapy, Active Treatment vs. Placebo
  - Regimen: A therapy being investigated; includes active and matched placebo
  - Shared placebo among all regimens
  - Uses concurrent and non-concurrent controls
  - Inclusion/Exclusion: Broad ALS patient population
- **Adaptive Trial**

Master Protocol Primary Analysis

Bayesian Repeated Measures of ALSFRS-R

- Model the linear rate of progression in ALSFRS-R for control participants
- **Treatment Effect:**

  Percent Slowing in the rate of progression relative to control

- **Increases power relative to simplified analyses**

- **Accommodates additional platform complexities**
  - Regimen-level differences of control arm
  - Time-trend effects in rate of progression of control arm
  - Covariates: ALSFRS-R baseline value and pre-slope
  - Mortality: Exponential proportional hazards time to event with shared treatment effect

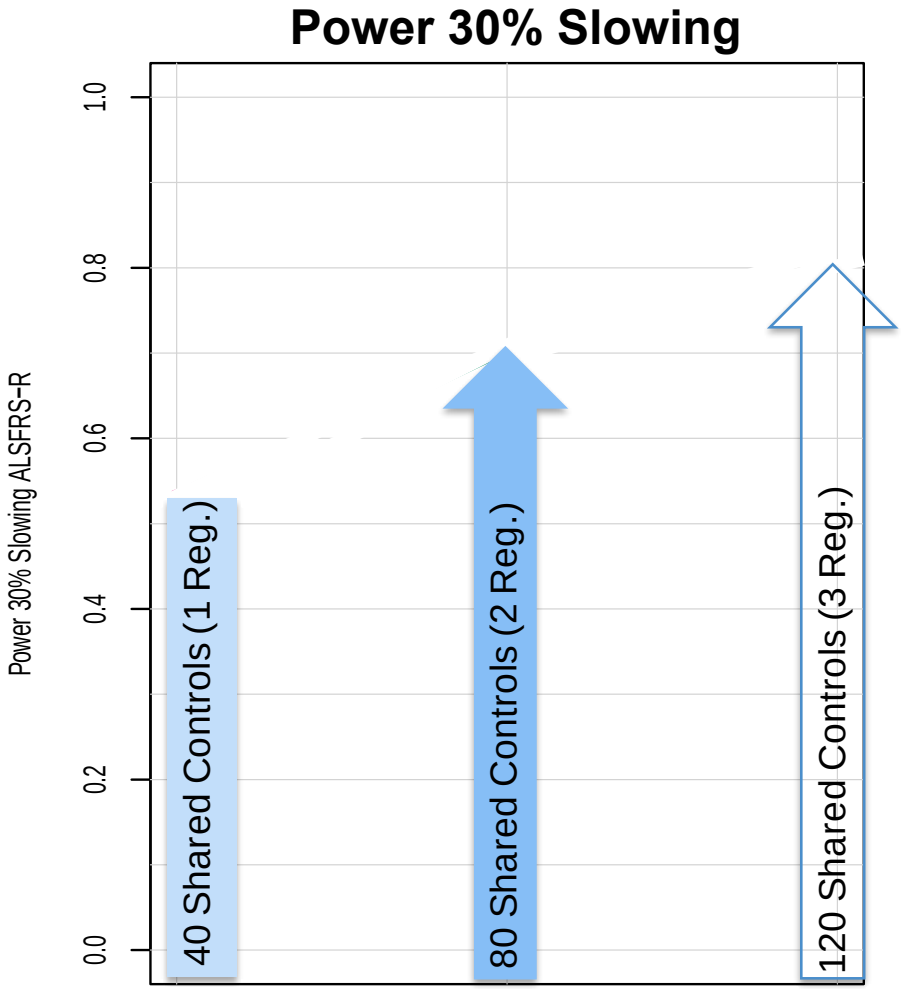
Shared Control Across Regimens

Share ALL controls across all regimens including:

- Different modes of administration
- Minor differences in inclusion /exclusion
- Concurrent and non-currently randomized

Analysis Model accounts for:

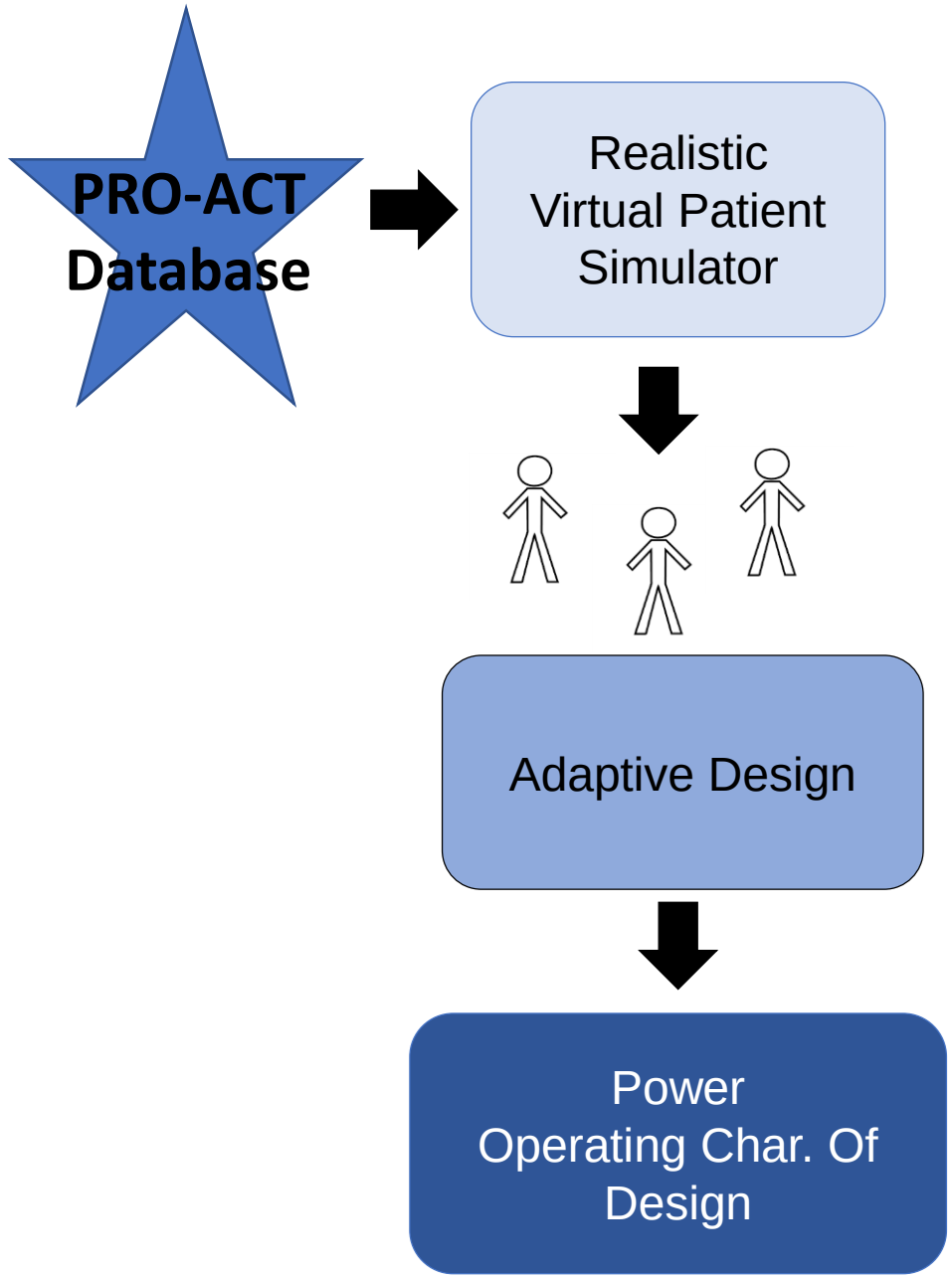
- Differences in controls over time in analysis (time-trend effect)
  - Concurrent vs. non-concurrently randomized controls
- Potential additional unexplained differences in controls across regimens (regimen-specific random effect)
  - Mode of administration
  - Different minor inclusion/exclusion



**N=160 per Regimen; 3:1 Rand.; Type I Error: 2.5%*

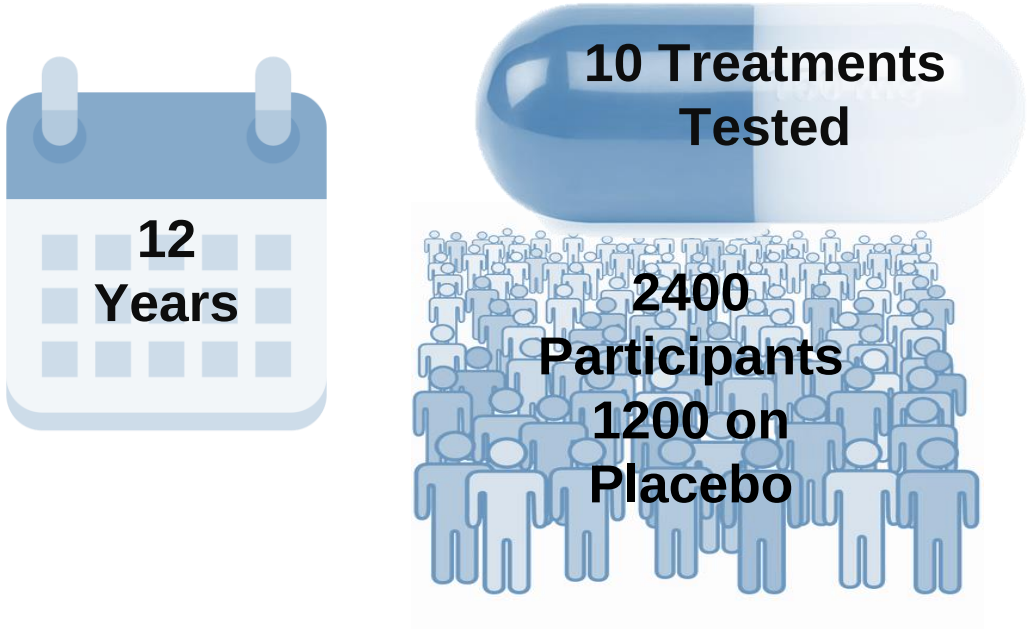
Clinical Trial Simulation

- Understand operating characteristics of proposed design
- Optimize design under key trial parameters
- Quantify Efficiencies of Proposed Platform Trial over Traditional

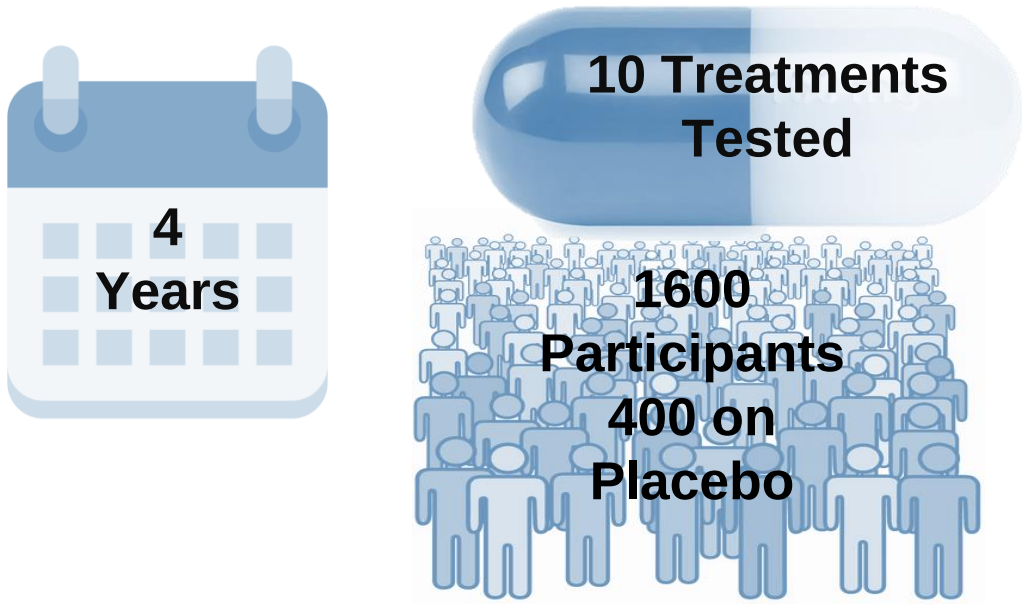


When will we find the first effective treatment?

- **Traditional Drug Development**
  - Sequence of fixed 1:1 trials
  - Each N=240 with 120 treated and 120 placebo
  - Lag of 3 months between trials



- **Adaptive Platform Trial**
  - Perpetually enrolling max. of 3 regimens
  - Max N=160 with 120 treated and 40 controls
  - Shared controls across regimens



**Assumes 10% of therapies tested are effective with a 30% slowing in rate of progression*

Summary

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

Platform trials can greatly accelerate the path to effective treatments for ALS

There is strong support for the platform approach - regulators, industry, clinician scientists, and patients

This is a perpetual trial and will continue to test more interventions until cures are found for all people with ALS

To participate:

https://www.massgeneral.org/neurology/als/research/platform-trial

Healey Center

Sean M. Healey & AMG Center
for ALS at Mass General

NEALS
Northeast Amyotrophic Lateral Sclerosis Consortium

Berry Consultants
Statistical Innovation

NCRI
NEUROLOGICAL CLINICAL RESEARCH INSTITUTE

BARROW
Neurological Institute

MGH 1811
MASSACHUSETTS GENERAL HOSPITAL

TACKLE ALS
"DONT BE SORRY LETS BEAT THIS"

ALS ONE

CLene NANOMEDICINE

Ra Pharma

biohaven pharmaceuticals

HARVARD MEDICAL SCHOOL

prilenia

Implicit BIOSCIENCE

To Participate:

https://www.massgeneral.org/neurology/als/research/platform-trial